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16. ABSTRACT

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To further examine the adrenal enlargement found in the reproduction study, an acute toxicity study was undertaken in which immature females were given ip injections of 0, 250, or 500 mg/kg TCB on 3 consecutive days. It was found that TCB had no estrogenic activity and that the livers and adrenals of treated females were significantly larger than those of controls. Rather than being estrogenic, TCB in this treatment regimen resulted in a decrease in uterine weight. These two studies demonstrate that chronic or acute doses of TCB can produce adrenal enlargement in rats.

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MULTIGENERATION STUDY OF 1,2,4-TRICHLOROBENZENE IN RATS

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Rats were continuously exposed to 0, 25, 100, or 400 ppm 1,2,4-trichlorobenzene (TCB) in the drinking water, beginning with birth of the F_0 generation and continuing through weaning of the F_2 generation. The treatment did not affect fertility, growth, viability, locomotor activity, or blood chemical analyses. Adrenal gland enlargement was observed in both the F_0 and F_1 animals at 95 d of age.

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INTRODUCTION

1,2,4-Trichlorobenzene (TCB) is present in the environment as a result of a variety of industrial processes. TCB is used as a dye carrier (Jones, 1973), dielectric and solvent (Dow Chemical, 1979), herbicide intermediate (Dow Chemical, 1975), fire retardant, and oil (Hawley, 1977). It is also used as a herbicide and a soil poison for termite control. TCB and other chlorinated benzenes also result from the breakdown of less stable pesticides such as hexachlorobenzene (Jondorf et al., 1955).

In 1975, total U.S. production of TCB was 8.8×10^8 g. The National Institute for Occupational Safety and Health estimates that 86,340 people per year are exposed to TCB in the workplace (NIOSH, 1979); however, Dow Chemical's estimates are much lower (Dow Chemical, 1979). TCB is considered slowly biodegradable (Simmons et al., 1977); however, concern about its possible health effects has been raised by recent studies that identified TCB in drinking water supplies and wastewater discharges (Gaffney, 1976) and in the tissues of freshwater fish (Veith et al., 1979).

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The acute toxicity of TCB has been shown to be relatively low, with an oral LD_{50} of 756 and 766 mg/kg in rats and mice, respectively (NIOSH, 1974). The chronic toxicity has been evaluated following dermal, inhalation, and oral exposures. Chronic topical applications of 5, 25, or 100% TCB to the ears of rabbits were reported to cause dose-related dermal irritation, but no systemic toxicity (Powers et al., 1975). Inhalation exposure to 25, 50, or 100 ppm TCB for 26 wk produced renal hepatocytomegaly and hyaline degeneration in the rats examined at 4 and 13 wk, but no damage was found at 26 wk. No damage was found at any time in male monkeys and rabbits exposed to identical inhalation treatments (Coate et al., 1977). Daily oral doses of 173.6 mg/kg TCB in monkeys caused hepatic induction followed by death in 20–30 d, while similar dosing with 25 mg/kg was nontoxic (Smith et al., 1978).

In adult male rats, 10–40 mg/kg·d TCB induced xenobiotic metabolism. Cytochrome c reductase and cytochrome P-450 levels were elevated and remained so during a 30-d recovery period (Carlson and Tardiff, 1976). Although TCB was found to be nonmutagenic in a study with the Ames test, it was confirmed that TCB is a potent inducer of liver metabolism (Schoeny et al., 1979).

Although much is known about the effects of TCB on liver function, a search of the literature revealed no studies that evaluated the potential of TCB to induce reproductive or teratogenic effects. The present study was conducted to determine whether chronic exposure to TCB in the drinking water, the major route of exposure in humans, would have an effect on reproduction or development in rats.

METHOD

One hundred, 90-d-old, timed-pregnant animals were obtained from the Charles River Breeding Laboratory, Wilmington, Mass. Upon arrival, all animals were housed individually in 43 × 23 × 20 cm plastic cages on pine shavings bedding in a temperature-controlled (22–26°C) and light-controlled (12 h light, 12 h dark) bioclean room. Throughout the study, animals were fed commercial laboratory diet *ad libitum.*

The timed-pregnant animals received tap water *ad libitum* until birth of the F_0 generation, when they were randomly assigned to one of five treatment groups and given the appropriate treated water. In all generations, each treatment group consisted of 17–23 litters. Dosage groups received 0, 25, 100, or 400 ppm TCB (Eastman-Kodak Co., Rochester, N.Y.). Because TCB is not soluble in water at the concentrations used, the TCB solutions also contained a solubilizer, Tween 20 (Fisher Scientific Co., Pittsburgh, Pa.), at a concentration of 0.125%. Another control group receiving 0.125% Tween 20 in the drinking water was included in the experimental design. No TCB precipitated from these preparations over at least a 1-wk period. The water used in the experiment was purified with a

Corning LD-5 glass still equipped with a 3508-ORC organic removal cartridge and a Corning 3508-B demineralizer. Animals were given freshly prepared solutions at least twice weekly and allowed to drink *ad libitum*.

At birth of the F_0 generation, litters were randomly reduced to 4 males and 4 females. Maternal weights, litter size, neonate sex and weights, and 24-h food and water intake were recorded on d 1, 8, 15, and 22. Litters were weaned at 25 d of age and housed as unisexual littermates. Body weights and 24-h food and water intake were measured on d 29, 35, 43, 50, and 83. Individual locomotor activity was measured for 12–20 animals per treatment group on d 16, 27, 48, and 90 by placing individual animals in a residential maze (Reiter et al., 1977) for 45 min. These ages were selected to represent the principal stages of sexual maturation (prepubertal, <35 d; early pubertal, 35–50 d; and adult, >50 d). Blood and organs were obtained from 10 males and 10 females per treatment group (approximately one animal per litter was used) at 37 and 95 d of age after anesthetization with sodium pentobarbital (ip, 36 mg/kg). The liver, lungs, heart, kidneys, adrenals, and gonads, as well as the seminal vesicles in the males, were removed and weighed. Blood samples were collected in Vacutainer tubes by cardiac puncture and centrifuged at 3000 X *g* for 10 min. The serum was removed, frozen, and later analyzed for glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, uric acid, calcium, phosphorus, cholesterol, triglyceride, bilirubin, alkaline phosphatase, serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic transaminase, creatinine phosphokinase, lactic dehydrogenase, total protein, albumin, and globulin by Smith Kline Clinical Laboratories (Creve Coeur, Mo.).

At approximately 90 d in the F_0 and F_1 generations, 12 breeding cages, each having 2 females and 1 male (within treatment nonsiblings), were established per treatment group for production of the subsequent generation. After 2 wk of cohabitation, the males were euthanized and the females were housed individually. The F_1 litters were reduced to 3 males and 4 females at weaning. The experiment was terminated when the F_2 animals were 32 d old, at which time the females were examined for vaginal opening.

Data collection procedures for the F_1 and F_2 generations were the same as described for the F_0 with the following exceptions: (1) preweaning growth and dietary intake measurements were recorded for the F_1 and F_2 generations on d 1 and 12; (2) postweaning growth and dietary intake measurements for the F_1 generation were made on d 25, 53, and 80; (3) residential maze activity was measured at 31 and 90 d in the F_1 and at 26 d in the F_2 generation; (4) blood samples and organ weights were taken only at 95 d in the F_1 generation; and (5) during the 95-d organ collection in the F_1 generation the livers and kidneys from Tween 20 and 400 ppm animals were preserved in neutral buffered Formalin. Subsequently, the tissue sections were prepared, stained with hematoxylin and eosin, and examined microscopically.

For preweaning growth and dietary intake measurements, the litter was regarded as the experimental unit. For postweaning growth and dietary intake measurements as well as for locomotor activity, organ weights, and blood chemistry data, the individual was considered the experimental unit. Since the vehicle was found to have a significant effect on one of the measured parameters (see Results), the Tween 20 control group was used as the zero dosage group in all statistical comparisons and is the zero dosage group shown in the tables unless stated otherwise. The significance of treatment-related effects was analyzed by analysis of variance and, when results were significant, by linear regression. Whenever a significant dose response was found by linear regression, Dunn's procedure was used to determine the significance of pairwise comparisons. The organ weight and blood chemistry data in the F_0 and F_1 generations at 95 d were analyzed by regression procedures as a 2 X 2 X 4 (sex, generation, dose) factorial design.

To further examine the TCB-related adrenal enlargement found in the reproduction study, an additional acute toxicity study was conducted. Since it is known that ovarian estrogens, as well as exogenous estrogenic compounds, stimulate adrenal growth in the rat, the acute toxicity study was used to determine whether the observed adrenal enlargement could have been due to estrogenic activity of TCB. With the procedures described by Hammond et al. (1979), administration of estrogenic compounds produces an increase in uterine weight in preweanling females. Weighing the adrenals made it possible to determine whether adrenal enlargement could be produced with acute doses of TCB. For this study, groups of 9–10 preweanling females were given ip injections of 0, 250, or 500 mg/kg TCB at 22, 23, and 24 d of age. The TCB was dissolved in corn oil. All injection volumes were 0.1 ml and controls received vehicle alone. The animals received tap water *ad libitum* and were otherwise maintained under the same conditions described for the reproduction study. At 25 d of age, body weights were recorded. The animals were then decapitated and the uterus, ovaries, liver, kidneys, and adrenals were removed and weighed. These data were analyzed by analysis of variance and linear regression procedures and, when results were significant, by Dunn's procedure.

RESULTS

Fertility, Growth, and Mortality

The gestation index (number of females delivering divided by number of females bred) and the data on preweaning litter size and mortality are presented in Table 1. The fertility of the F_0 and F_1 animals bred for the subsequent generation was not affected by the treatment. The treated F_2 females did not differ significantly from controls in the time of vaginal opening. No significant dose-related differences were found in neonate

TABLE 1. Effects of TCB on Fertility and Neonatal Survival

Dose (ppm TCB)	Females delivering / Females bred		Litter size, d 1		Percent mortality to d 12		Percent mortality from d 12 to weaning	
	F_0	F_1	F_1	F_2	F_1	F_2	F_1	F_2
0 (water)	23/24	18/24	13.3 ± 0.94[a]	9.8 ± 0.64	15.0 ± 3.42	6.3 ± 2.96	3.3 ± 2.20	1.0 ± 0.70
0 (Tween 20)	22/24	19/24	12.8 ± 0.71	10.3 ± 0.87	14.2 ± 3.46	9.3 ± 5.62	1.2 ± 0.92	3.6 ± 2.74
25	19/24	21/24	14.5 ± 0.42	10.5 ± 0.98	21.3 ± 5.02	3.7 ± 2.50	2.0 ± 0.97	0.8 ± 0.62
100	18/24	17/24	13.4 ± 0.80	12.8 ± 0.88	21.8 ± 6.77	5.7 ± 2.19	3.2 ± 1.63	1.2 ± 0.69
400	22/24	20/24	14.1 ± 0.36	12.8 ± 0.78	13.1 ± 4.00	5.4 ± 2.33	4.3 ± 2.47	3.0 ± 1.34

[a]Values are means ± SE.

TABLE 2. Representative Dietary Intake Data from the F_0 Generation with Calculated Dosages

Dose (ppm TCB)	Female food intake (g/d per animal)	Female water intake (ml/d per animal)	Calculated female dosage (mg/kg • d TCB)	Male food intake (g/d per animal)	Male water intake (ml/d per animal)	Calculated male dosage (mg/kg • d TCB)
			29 d of age			
0	13.9 ± 0.4[a]	24.4 ± 1.3		17.4 ± 0.5	26.9 ± 1.1	
25	14.4 ± 0.6	28.5 ± 2.5	8.3 ± 0.8	15.7 ± 0.8	31.9 ± 2.1	8.5 ± 0.6
100	13.4 ± 0.2	24.8 ± 0.9	28.0 ± 1.2	16.5 ± 0.6	27.2 ± 1.6	27.6 ± 1.6
400	14.1 ± 0.3	27.3 ± 2.2	133.2 ± 13.4	19.3 ± 1.8[b]	32.1 ± 3.4	133.6 ± 15.6
			83 d of age			
0	20.0 ± 0.7	31.6 ± 1.6		31.7 ± 0.8	43.9 ± 1.8	
25	20.0 ± 0.7	31.6 ± 1.3	3.7 ± 0.1	30.6 ± 1.0	47.0 ± 2.2	2.5 ± 0.1
100	20.0 ± 0.8	30.8 ± 1.7	14.8 ± 1.0	30.9 ± 1.2	42.0 ± 1.3	8.9 ± 0.3
400	19.6 ± 0.8	26.2 ± 0.8[b]	53.6 ± 3.9	29.3 ± 0.6	38.6 ± 1.7[b]	33.0 ± 1.4

[a]Values are means ± SE.
[b]Significantly different from controls, $p < 0.05$.

weight, maternal weight, litter size, or viability during the preweaning period in any generation. The postweaning growth of the F_0 and F_1 animals was not affected by TCB.

Dietary Intake

Representative dietary intake data are presented in Table 2 along with the calculated dosages for each treatment group. While no treatment-related changes in food and water intake were found in any generation during the preweaning period, a treatment-related increase in food intake was found in the F_0 males at 29 d [$F(1,59) = 4.97, p < 0.028$]. There were also two instances of a treatment-related decrease in water intake in the F_0 generation, one in the females at 35 d [$F(1,80) = 5.71, p < 0.018$] and another in both sexes at 83 d [males, $F(1,68) = 11.72, p < 0.001$; females, $F(1,68) = 15.05, p < 0.001$]. In all three of these dietary effects in the F_0 generation, Dunn's procedure found only the high-dose group to be significantly different from controls. No treatment-related differences in food or water intake were found in the F_1 generation during the postweaning period.

Locomotor Activity

Although normal sex and age differences were reflected in the residential maze activity measurements, no treatment effect was found at any time the measurements were taken. The data, presented in Table 3, show that

TABLE 3. Locomotor Activity of Animals Exposed to TCB

Generation	Age (d)	Sex	Dose (ppm TCB) 0	25	100	400
F_0	16	M	227 ± 19.3[a]	246 ± 19.6	184 ± 30.7	207 ± 16.9
		F	292 ± 44.2	233 ± 36.2	202 ± 35.7	253 ± 34.3
F_0	27	M	418 ± 36.8	390 ± 40.0	459 ± 31.5	428 ± 19.6
		F	429 ± 25.4	427 ± 23.5	388 ± 18.1	438 ± 24.0
F_0	48	M	620 ± 42.7	744 ± 46.9	633 ± 62.5	633 ± 59.5
		F	701 ± 37.7	778 ± 86.7	772 ± 38.5	811 ± 61.4
F_0	90	M	611 ± 70.9	678 ± 44.0	556 ± 69.4	772 ± 70.0
		F	746 ± 65.0	796 ± 58.7	746 ± 42.8	888 ± 65.7
F_1	31	M	555 ± 49.3	510 ± 40.7	500 ± 59.3	472 ± 48.7
		F	467 ± 63.2	556 ± 40.7	462 ± 51.3	578 ± 48.7
F_1	90	M	611 ± 46.4	590 ± 110.9	596 ± 45.0	586 ± 55.7
		F	728 ± 82.9	802 ± 58.8	712 ± 91.3	784 ± 77.5
F_2	26	M	394 ± 30.8	373 ± 28.5	282 ± 14.6	387 ± 41.4
		F	286 ± 44.2	359 ± 88.5	344 ± 58.1	373 ± 70.0

[a]Number of photocells interrupted in a 45-min session; mean ± SE.

males and females have similar activity measurements in the prepubertal period, that both sexes become more active with age, and that females are consistently more active than males after sexual maturation.

Organ Weights, Histology, and Blood Chemistry

Of the organs weighed in this study, only the adrenals were significantly affected by TCB. As shown in Table 4, the 400 ppm TCB dose produced significantly enlarged adrenals in both sexes in the F_0 and F_1 animals at 95 d of age [$F(1,154) = 7.68, p < 0.006$]. The vehicle, Tween 20, caused a significant increase in kidney weight in the F_0 and F_1 animals at 95 d [$F(1,73) = 6.92, p < 0.010$]. There was also a significant vehicle X sex interaction [$F(1,73) = 11.75, p < 0.001$]; as shown in Table 5, the male kidneys were affected to a greater extent by the Tween 20 than were the female kidneys. Kidney weight was the only parameter in this study for which a significant difference between the water and Tween 20 control groups was observed. No histological damage was found in the livers or kidneys of the F_1 generation animals examined at 95 d of age. No dose-related changes were found in the blood chemistry analyses at any sampling time.

Gross Pathology

Two isolated cases of disease were found. In each case, the animals involved were examined by a veterinary pathologist. A spontaneous

TABLE 4. Effect of TCB in the Drinking Water on Adrenal Weights

Dose (ppm TCB)	Males	Females
	F_0, 95 d	
0 (water)	28.7 ± 1.78[a]	34.1 ± 1.87
0 (Tween 20)	28.6 ± 1.09	36.8 ± 1.14
25	28.8 ± 1.59	35.6 ± 1.70
100	28.2 ± 1.10	36.6 ± 1.08
400	31.8 ± 2.43[b]	41.5 ± 1.99[b]
	F_1, 95 d	
0 (water)	27.1 ± 1.71	35.8 ± 1.89
0 (Tween 20)	28.0 ± 1.57	37.0 ± 1.36
25	28.8 ± 1.46	34.8 ± 1.77
100	26.6 ± 0.82	35.3 ± 1.07
400	29.6 ± 1.66[b]	38.5 ± 1.89[b]

[a]Values are means ± SE; weights are in milligrams and for the left adrenal only.
[b]Significantly different from controls, $p < 0.05$.

TABLE 5. Tween 20 Effect on Kidney Weight at 95 d

	F_0		F_1	
Control group	Males	Females	Males	Females
Water	1.65 ± 0.081[a]	1.04 ± 0.035	1.62 ± 0.065	1.00 ± 0.043
Tween 20	1.81 ± 0.059[b]	1.06 ± 0.044	1.88 ± 0.070[b]	1.03 ± 0.023

[a]Values are means ± SE; weights are in grams.
[b]Significantly different from water control group, $p < 0.05$.

lymphoma was the cause of death in a 32-d-old F_1 male in the 100 ppm group and a case of hydrocephaly was found in a 24-d-old F_2 male in the 400 ppm group.

Acute Toxicity

The results of the study in which preweanling females received three daily ip injections of TCB are shown in Table 6. In this experiment, the following dose-related changes were found: (1) a decrease in body weight [$F(1,27) = 9.76$, $p < 0.004$], (2) a decrease in uterus weight [$F(1,27) = 8.36$, $p < 0.007$], (3) an increase in liver weight [$F(1,27) = 28.04$, $p < 0.0001$], and (4) an increase in adrenal weight [$F(1,27) = 15.67$, $p < 0.001$].

DISCUSSION

The results of this study indicate that TCB does not affect growth, viability, or reproductive function in rats when administered in the drinking water at concentrations far above those found in the environment. Although statistically significant, the treatment-related changes in the food and water intake did not occur consistently and were only found in one generation. The blood chemistry analyses and locomotor activity measurements revealed no overt hematological or neurological disorders related to the treatment.

The enlarged adrenals found in both sexes and both generations at 95 d of age were the only significant and persistent TCB-related developmental effect found in the reproduction study. The results of the acute toxicity study show that adrenal enlargement can also be produced with acute doses of TCB and that TCB has no estrogenic activity. Although no cause for the adrenal enlargement can be determined at present, the acute toxicity study clarifies two possible causes for the adrenal effect found in the reproduction study. First, the adrenal enlargement was not due to estrogenic properties of TCB. Second, the effect was not necessarily caused by some form of long-term stress, such as a stress related to drinking the treated water, since the adrenal enlargement can be produced

TABLE 6. Effect of Acute Exposure to TCB on Organ Weight

Dose (mg/kg TCB)	Weight					
	Body (g)	Uterus (mg)	Ovary[a] (mg)	Liver (g)	Kidney[a] (g)	Adrenal[a] (mg)
0	68.1 ± 1.9[b]	38.6 ± 1.7	14.0 ± 0.4	3.13 ± 0.13	0.37 ± 0.01	7.9 ± 0.5
250	64.5 ± 4.5	30.4 ± 1.6[c]	14.0 ± 0.7	4.14 ± 0.24[c]	0.37 ± 0.02	9.6 ± 0.5
500	55.2 ± 2.9[c]	31.6 ± 1.7[c]	13.0 ± 0.9	4.34 ± 0.15[c]	0.38 ± 0.02	10.4 ± 0.5[c]

[a]Weights are for the left organ only.
[b]Values are means ± SE.
[c]Significantly different from controls, $p < 0.05$.

with acute doses of TCB. The treatment-related increase in liver weight found in the acute study probably reflects the previously reported potential of TCB to induce liver metabolism (Schoeny et al., 1979; Smith et al., 1978). The reduction in uterine weight observed in immature females exposed to TCB might be due to decreased circulating levels of estrogens as a result of this increased liver metabolism.

Although the adrenal enlargement found in the reproduction study was a significant developmental effect caused by TCB in the drinking water, it must be noted that this effect only occurred in the 400 ppm group and that even the 25 and 100 ppm concentrations used in this study were far above concentrations of TCB found in the environment. This study found no evidence that TCB in the drinking water decreases survival or affects reproduction in rats.

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